REMARKS

Claims 1-47 were pending prior to this response, with claims 11-47 being withdrawn in response to a restriction requirement. By the present communication, the portion of Table 1 on page 10 has been amended to remove an embedded hyperlink. In addition, claims 11-47 have been cancelled without prejudice, no claims have been added, and claim 1 has been amended to define Applicants' invention with greater particularity. No new matter is added by the claim amendment, being fully supported by the Specification and original claims. Accordingly, claims 1-10 are currently pending.

The Objection to the Specification

The Office Action indicates that the disclosure is objected to for allegedly containing an embedded hyperlink and/or other form of browser-executable code at page 10. By the present communication, page 10 has been amended to delete the embedded hyperlink in the portion of Table 1 on page 10. Accordingly, Applicants submit that the amended disclosure meets all requirements under MPEP § 608.01 and reconsideration and withdrawal of the objection to the Specification are respectfully requested.

The Rejection under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 1, 7 and 9 under 35 U.S.C. § 103 for allegedly being unpatentable over the disclosure of Glickman et al. (1998; hereinafter "Glickman") in view of U.S. Patent No. 6,165,731 to Deshaies et al. (hereinafter "Deshaies"). Applicants respectfully submit that the invention methods of deconjugating in proximity to a metal ion a modifier protein from a target protein, wherein the modifier protein is conjugated to the target protein via a peptide bond between the carboxy terminus of the modifier protein and a free amino group of the target protein, as defined by amended claim 1, distinguish over the combined disclosures of Glickman and Deshaies by requiring: "contacting the peptide bond with a polypeptide comprising a metalloprotease characterized as a JAB subunit."

Applicants submit that Glickman is absolutely silent regarding a method of deconjugating a modifier protein from a target protein, wherein the modifier protein is conjugated to the target protein via a peptide bond between the carboxy terminus of the modifier protein and a free amino group of the target protein and wherein the deconjugation requires proximity to a metal ion. In addition, Glickman fails to disclose that the protein subunit responsible for accomplishing the deconjugation is an isopeptidase that functions only in proximity to a metal ion, in other words, that JAB1 is a novel metallo-isopeptidase. Although Glickman purports to describe the active site in the Rpn11/Mpr1 protein (Glickman page 3153 final paragraph), the description was in error, an error that those of skill in the art were quick to point out, as Applicant will detail below. Thus, Applicants submit that Glickman is silent regarding any method for deconjugating a modifier protein from a target protein that involves hydrolyzing a peptide bond "between the carboxy terminus of the modifier protein and a free amino group of the target protein in proximity to a metal ion."

To cure the deficiencies of Glickman for suggesting the invention methods, the Examiner relies upon Deshaies as disclosing that "ubiquitination is an important process in cell cycle regulation [such that] modifying unstated proteins with ubiquitin regulates their activity" (Office Action, page 3). However, Deshaies' disclosure is focused on the process involved in attaching ubiquitin to a "substrate," not the process of deconjugating the modifier ubiquitin from the substrate. Accordingly, Deshaies describes the process of deconjugation in vague terms. For example, Deshaies states: "The ubiquitinated SIC1p is then targeted for degradation by *a ubiquitin dependent protease*" (Col. 6, lines 36-38; emphasis added). "Cyclins E and D1 are degraded by a ubiquitin-dependent pathway following phosphorylation at a specific site" (Col. 3, lines 38-40). Therefore, Applicants respectfully submit that Deshaies' comments fail to provide any suggestion as to the structure of the ubiquitin-dependent pathway, the mechanism by which a deconjugating enzyme works, or the structure of the enzymatic site in the conjugate.

Therefore, Applicants submit that the combined disclosures of Glickman and Deshaies would not motivate those of skill in the art to understand that ubiquitin is one

example of a "modifier protein" whose attachment to a substrate controls cell cycling or that modification of such control can be achieved by deconjugating the "modifier protein" "via a peptide bond between the carboxy terminus of the modifier protein and a free amino group of the target protein". In addition, there is no suggestion at all in the combined disclosures of the cited art that the method of deconjugation utilizes a metalloprotease characterized as a JAB subunit because both Glickman and Deshaies are silent regarding metalloprotease activity in any context.

Moreover, Applicants respectfully submit that even if the combined disclosures of Glickman and Deshaies were sufficient to motivate those of skill in the art "to try" the invention methods there would be no reasonable expectation of success because at the time the final draft of Glickman's paper was accepted for publication, it was not yet known that the cullin subunit of SCF is modified by Nedd8. In fact, it had been incorrectly reported by the Tyers group in 1996 that cullin is modified by ubiquitin. In addition, the molecular identification of mammalian COP9 Signalosome subunits and the similarity of COP9 Signalosome to the proteasome was not reported until July of 1998. Thus, at the time of Glickman's finding, those skilled in the art could not have concluded that the COP 9/Signalosome polypeptide must be cleaving Nedd8 from cullin or deconjugating any other modifier protein from a target protein, wherein the modifier protein is conjugated to the target protein via a peptide bond between the carboxy terminus of the modifier protein and a free amino group of the target protein in proximity to a metal ion.

Moreover, Glickman is in error in proposing, based on a sequence alignment suggesting the existence of a conserved cysteine in a region with limited homology to other deubiquitinating enzymes, that Rpn11 might be a cysteine-based deubiquitinating enzyme. It has been shown that this alignment is bogus on theoretical grounds and in their publication Cope et al (*Science* 298(5593):608-11, Oct 2002, a copy of which is attached) showed that the mutation of the cysteine identified by Glickman had no effect on Nedd8 isopeptidase activity. Glickman's group reached the same conclusion and reported in a recent paper that the conserved Cys116 residue "does not appear to be an

essential residue in Rpn11" (Kivity V, et al., *BMC Biochem.* 3:28, 2002, see abstract, a copy of the reference is attached, see page 4 of 12). Thus, the structural basis for the original suggestion made in Glickman (1998) that Rpn11 is a cysteine-based deubiquitinating enzyme has been refuted by those of skill in the art.

Moreover, the cited Glickman reference suggests its own error, a suggestion completely overlooked by the Examiner in the cited reference. Glickman states: "our proteasome preparations had low activity in several deubiquitinating assays" (Glickman, p 3158, penultimate paragraph). In the next sentence Glickman admits there is no evidence that the deubiquitinating activity shown is Rpn11-dependent. The most recent publication from Glickman's lab reaches the conclusion that the deubiquitinating activity seen in the proteasome preparation stems from Ubp6, not Rpn11. Moreover, data in R. Verma et al. unambiguously showed that Ubp6 deubiquitinating activity is irrelevant to deubiquitinating of a proteasome substrate (Science (2002) 298:611-615 and online published supplement to Verma et al., a pdf copy of which is attached).

Accordingly, Applicants submit that those of skill in the art who read Glickman with care would not have been motivated by the combination of Glickman and Deshaies to arrive at the invention methods. Clearly, those of skill in the art were quick to point out Glickman's errors. Even if others of skill in the art had been so motivated, Applicants submit that in view of Glickman's doubt that the deubiquitinating activity shown is actually Rpn11-dependent (referred to above), there would not have been a reasonable expectation that a broad range of biological processes dependent upon conjugation and deconjugation of a modifier protein, such as ubiquitin or Nedd8, could be modified by utilizing an Rpn11-type molecule. Especially, there would have been no reasonable expectation that a broad range of biological processes could be modulated by contacting the peptide bond joining a modifier protein and a target protein, as required by Applicants' claims, with a polypeptide comprising the structural features of a JAB subunit because the combined disclosures of Glickman and Deshaies fail to disclose the claimed substrate site for which the isopeptidase has activity.

Therefore, Applicants respectfully submit that *prima facie* obviousness of the invention methods of deconjugating a modifier protein from a target protein, as required in claims 1, 7 and 9' is not established under 35 U.S.C. § 103 over the combined disclosures of Glickman and Deshaies, and reconsideration and withdrawal of the rejection are respectfully requested.

The Objection to the Claims

Applicants respectfully traverse the objection to claims 2-6 and 8 as being dependent upon a rejected base claim. In view of the remarks above, Applicants respectfully submit that grounds for the rejection of claim 1, from which claims 2-6 and 8 depend, has been overcome for the reasons above stated. Accordingly, Applicants respectfully request reconsideration and withdrawal of the objection to claims 2-6 and 8.

In view of the above amendments and remarks, reconsideration and favorable action on claims 1-10 are respectfully requested. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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Enclosures:
Publication of Cope et al.
Publication of Verma et al.